Original Article

Effect of injection laryngoplasty material on outcomes in pediatric vocal fold paralysis

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Background: While injection laryngoplasty is becoming increasingly common in children, there has not been clearly established guidelines for the choice of injection material. This study evaluates for variability in post-surgical outcomes between different materials used for injection laryngoplasty in the treatment of pediatric unilateral vocal cord paralysis.

Methods: In this cohort study, a retrospective chart review was performed for all patients undergoing injection laryngoplasty for unilateral vocal cord paralysis at our tertiary-care children's hospital between January 2010 and December 2019. Patients with vocal cord paresis or bilateral vocal cord paralysis were excluded from this study. Demographics, pre- and post-injection clinic visits, and operative reports were reviewed to compare outcomes between injection materials, including the number of injections required, inter-surgical interval, and rate of vocal improvement.

Results: Forty-four patients were included in the analysis. Half of the patients were female, and half were male. A total of 97 injections were observed, with 32 patients receiving multiple injections. The mean age at first injection was 7 years. The most common causes of vocal fold paralysis were iatrogenic (n=21, 48%) and idiopathic (n=9, 20%). Thirty-nine percent (n=17) had a history of cardiac surgery. Forty-five percent of injections used Radiesse® voice/Prolaryn® plus, 35% used Radiesse®/Prolaryn® voice Gel, and 20% used Cymetra™. The material used was not associated with a difference in post-operative outcomes, including number of injections, (P=0.10; 0.29), inter-surgical interval (P=0.27; 0.29), or rate of voice improvement (P=0.86; 0.36).

Conclusions: Neither material choice nor demographic factors were associated with a difference in outcomes following injection laryngoplasty or a change in the inter-surgical interval. Further research is needed to develop standardized protocols for injection laryngoplasty in this population.

Keywords: Vocal cord augmentation; injection laryngoplasty; inter-surgical interval; unilateral vocal cord paralysis

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Introduction

Unilateral vocal cord paralysis (UVCP) is among the most common congenital laryngeal defects in the pediatric population, accounting for approximately 10% of all congenital laryngeal disorders. Whether congenital or acquired, vocal fold paralysis may affect a child's ability to breathe, speak, or swallow (1,2). Children with UVCP present with symptoms of dysphonia, aspiration, dysphagia, stridor, and difficulty breathing. Available treatments for this condition include voice therapy, injection laryngoplasty, medialization thyroplasty, laryngeal reinnervation, and tracheostomy (3,4).

While injection laryngoplasty (IL) is a commonly performed procedure for vocal fold paralysis in the adult population, this technique has historically been avoided in children due to the presence of a smaller larynx conferring a higher risk of post-injection airway obstruction (5). More recently however, IL has been shown to be a safe treatment modality for children with vocal fold paralysis, even in patients less than 6 months of age (6). This is a favorable alternative to more invasive procedures such as medialization thryoplasty due to its low-cost, availability, technical ease, and non-permanence in cases of reversible vocal fold paralysis (7).

At present, there are no clearly established guidelines for the choice of injection material in injection laryngoplasty. Commonly used materials include Cymetra™, a micronized dermal matrix shown to last an average of six weeks to six months, Radiesse® voice gel/Prolaryn® voice gel, an injectable aqueous/glycerin/carboxymethylcellulose gel implant that lasts approximately 2–6 months, and Radiesse® Voice/Prolaryn® Plus, which lasts approximately 12–24 months due to the addition of Calcium Hydroxyapatite (8-11). While the etiology of UVCP and anticipated required duration of medialization may help to guide the choice of material, the decision is often determined by provider or institutional preference. Further evidence comparing the post-injection outcomes between the various available injection materials is required to develop standardized protocols for injection laryngoplasty in the pediatric population.

In the present study, we compare post-operative outcomes between injection materials for patients undergoing injection laryngoplasty for unilateral vocal fold paralysis. Our outcomes of interest include the number of injections required, the inter-surgical interval, and rate of vocal improvement. Secondary objectives of the study include characteristics of the single injection population, characteristics associated with improvement in outcomes, differences in characteristics by etiology of the UVCP, and the impact of early intervention. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-21-361/rc).

Methods

Study population

Our study was reviewed and approved by Nationwide Children's Research Institute institutional review board. A retrospective chart review was conducted for all 44 patients who underwent laryngoscopy with vocal cord injection for UVCP between January 2010 and December 2019 at our tertiary care children's hospital. Patients were excluded from the study if they had vocal cord paresis or bilateral vocal cord paralysis.

Measures and outcomes

Medical records were reviewed for demographic data, comorbid conditions, IL procedure(s), follow up appointment(s), and diagnostic studies. Etiology of UVCP was reviewed. The material used for each injection, the time between injections, and the age at first injection were recorded. Improvement post-injection was defined as child or parental reported improvement in voice, swallowing, feeding tolerance, dietary advancement and/or improvement in post-operative swallowing studies when compared to baseline. Material used for IL at our institution were Cymetra™, Radiesse® Voice/Prolaryn® Plus, or Radiesse®/Prolaryn® voice Gel. IL was performed in the operating room under suspension laryngoscopy with microscopic or endoscopic visualization to achieve satisfactory medialization for all patients.

Statistical analysis

We present descriptive data for 44 patients who received vocal cord injections using percentages for categorical data and medians for continuous data. For bivariate comparisons at the unique patient level, Chi-squared tests were employed with two categorical variables, Pearson correlations were employed when both variables were continuous, and Anova and Wilcoxon Mann Whitney tests were employed when

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one variable was continuous and the other was categorical. To evaluate bivariate comparisons at the injection level, we employed multilevel regression models that included random effects to account for within-person variability given that several patients had multiple observations. Two tailed p-values were calculated for each comparison using SAS Enterprise Version 8.1 and statistical significance was evaluated at the 0.05 alpha level.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Nationwide Children's Hospital (No. 00000568) and individual consent for this retrospective analysis was waived.

Results

Forty-four patients received vocal cord injections for UVCP (*Table 1*). Half of patients were female, and the median age at first injection was 7 years. The most common causes of vocal fold paralysis were identified as iatrogenic (n=21, 48%) and idiopathic (n=9, 20%). Seventeen patients (39%) had a history of cardiac surgery. Presenting complaints included feeding difficulty or aspiration in 52% and dysphonia in 82%. Aspiration secondary to UVCP was most frequently diagnosed with video swallow study (57%). The median time between diagnosis and first injection was 164 days. The material most often used for the first injection was Radiesse®/Prolaryn® voice Gel (50%). Sixty-eight percent of patients experienced subjective and/or objective improvement compared to baseline following the initial injection, and 14% did not return for follow up. Patients had a median of 2 vocal cord injections, and 97 injections total were observed among the 44 patients. Among the 32 patients with more than one injection, 44% were injected with multiple different injection preparations.

Injection material

Of the 97 injections, 45% were performed using Radiesse® voice/Prolaryn® plus, 35% with Radiesse®/Prolaryn® voice Gel, and 20% with Cymetra™ (*Table 2*). The median age for patients receiving Radiesse®/Prolaryn® plus was younger (6 years) than patients receiving Cymetra™ (11 years, P<0.0001). Etiology of the UVCP was not associated with the material chosen, and we did not observe differences in material for patients with one single injection compared to those with multiple injections. No single material was associated with a higher rate of improvement at the follow up visit.

Inter-surgical interval (ISI)

The median ISI between injections was 356 days (Q1: 196, Q3: 651). Among patients with multiple injections, 54% were injected with a different material than the initial injection. The composition of the injected material was not associated with the ISI, suggesting that no material was associated with shorter or longer interval between injections (*Table 3*). No difference in ISI was observed for patients presenting with dysphonia *vs.* feeding difficulty *vs.* aspiration (*Table 3*). ISI was also not associated with the etiology of the UVCP. Patients with iatrogenic UVCP had median ISI of 371 days, compared to 420 days in patients with idiopathic UVCP (P=0.53). Age at first vocal cord injection was not associated with ISI (P=0.83). Similarly, early intervention (shorter time from diagnosis to first injection) was not associated with subsequent ISI (P=0.66). We observed that as the number of injections increased the ISI also increased (P=0.04).

Number of injections

Eighteen patients (41%) received only one vocal cord injection. These patients were similar in age and sex to patients requiring multiple injections. Patients who received a single injection were less likely to have presented with feeding difficulty or aspiration than patients who required multiple injections (28% *vs.* 69%, P=0.01). Conversely, no association was observed between patients presenting with dysphonia and number of injections. There were no differences in the history of cardiac disease or other relevant history. While 28% of single injection patients had Cymetra™, 4% of multiple injection patients had Cymetra™ on their first injection (P=0.04). No differences in the time from diagnosis to first injection were observed between single and multiple injection patients, and no differences in improvement following the first injection were observed between groups.

Treatment efficacy

Among all 97 injections, 74 (76%) experienced subjective and/or objective improvement compared to baseline, 15

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Table 1 Characteristics of patients with unilateral vocal cord paralysis undergoing vocal cord injection (n=44)

Characteristics	N (median)	% (Q1, Q3)
Total	44	100%
Sex		
Female	22	50%
Male	22	50%
Age at first injection, years	7	[5, 11]
Etiology		
Iatrogenic	21	48%
Idiopathic	9	20%
Upper airway abnormality	5	11%
Central nervous system neoplasms and malformations	4	9%
History of prolonged intubation	3	7%
Trauma	2	5%
History of cardiac surgery	17	39%
Presenting symptoms		
Feeding difficulty or aspiration	23	52%
Dysphonia	36	82%
Method of UVCP diagnosis		
Video	25	57%
Functional endoscopic evaluation of swallowing	5	11%
Clinical judgment	4	9%
Unknown	11	25%
Time from diagnosis to first injection, days	164	[55, 954]
Material of first injection		
Radiesse Voice/Prolaryn Plus	16	36%
Radiesse/Prolaryn Gel	22	50%
Cymetra	6	14%
Outcomes of first injection		
Improvement	30	68%
No improvement	8	18%
No follow-up data	6	14%
Number of injections	2	[1, 3]
Patient with injections with different materials (32 patients with more than 1 injection)	14	44%

UVCP, unilateral vocal cord paralysis.

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Table 2 Characteristics associated with material for vocal cord injection (n=97)

Characteristics	Cymetra			Radiesse/Prolaryn Voice Gel			Radiesse Voice/Prolaryn Plus		
	N (Median)	% (Q1, Q3)	P value	N (Median)	% (Q1, Q3)	P value	N (Median)	% (Q1, Q3)	P value
Total number of injections	19	20%	N/A	34	35%	N/A	44	45%	N/A
Median age at injection	11	[8, 15]	<0.0001	8	[5, 12]	0.40	6	[4, 11]	Ref
UVCP etiology									
Iatrogenic	12	25%	Ref	13	27%	Ref	23	48%	Ref
Idiopathic	3	14%	0.96	9	41%	0.92	10	45%	Ref
History of airway surgery	2	18%	0.93	2	18%	0.94	7	64%	Ref
Central nervous system neoplasms and malformations	1	20%	0.99	2	40%	0.98	2	40%	Ref
History of prolonged intubation	0	0%	N/A	6	86%	0.82	1	14%	Ref
Trauma	1	25%	0.96	2	50%	0.93	1	25%	Ref
Outcomes									
No improvement	2	13%	Ref	7	47%	Ref	6	40%	Ref
Improvement at follow up	14	19%	0.86	24	32%	0.36	36	49%	Ref
No follow up data	3	38%	N/A	3	38%	N/A	2	25%	N/A
Number of injections									
One	5	28%	Ref	6	33%	Ref	7	39%	Ref
More than one	1	4%	0.10	16	62%	0.29	9	35%	Ref

Ref, reference value used to calculate P value; N/A, not applicable; UVCP, unilateral vocal cord paralysis.

(15%) experienced no improvement, and 8 patients (8%) lacked follow-up data. Patients experiencing improvement were similar in age, sex, medical history, and presenting complaint to patients that did not experience improvement. The type of material injected was not associated with any significant differences in rate of treatment success. We did not observe that younger patients at the time of their first injection or patients with shorter duration between diagnosis and first injection demonstrate higher improvement rates for subsequent injections. In patients receiving multiple injections, changing the injected material was not associated with a higher rate of improvement.

Etiology of UVCP

Etiology was not associated with total number of injections or the ISI. Etiology was not associated with the injection material chosen. Etiology was also not associated with the time period between diagnosis and first injection.

Early intervention

Early intervention (shorter time from diagnosis to first injection) was not associated with the number of total injections or improvement in symptoms following injection.

Discussion

Treatment of UVCP in children may involve observation, speech therapy, injection laryngoplasty, or medialization thyroplasty. Individual management depends on the severity of the presentation, patient and caregiver preference, and expected outcome. IL has gained popularity in recent years as a safe and effective treatment for glottic insufficiency related to UVCP in children (7). Despite its efficacy, it is considered a temporary treatment modality and is primarily utilized to temporize patients until recovery of vocal fold function or a more permanent treatment modality is decided (12). While there are a variety of different injection

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Table 3 Characteristics associated with inter-surgical interval (n=53)

Characteristics	Inter-surgical interval (days)		
	Median	Q1, Q3	P value
Total	356	[196, 651]	N/A
Material			
Radiesse Voice/Prolaryn Plus	378	[221, 707]	Ref
Radiesse/Prolaryn Gel	287	[182, 491]	0.27
Cymetra	316	[206, 407]	0.29
Symptoms			
Feeding difficulty or aspiration	360	[182, 637]	0.65
Dysphonia	329	[182, 651]	0.69
Etiology			
Iatrogenic	371	[196, 651]	Ref
Idiopathic	420	[273, 735]	0.53
History of airway surgery	274	[98, 315]	0.51
Central nervous system neoplasms and malformations	273	[273, 273]	0.65
History of prolonged intubation	336	[165, 1,302]	0.21
Trauma	162	[71, 252]	0.32
Age at first injection, years			0.83
Age ≤7	350	[154, 658]	
Age >7	356	[252, 620]	
Early intervention			0.66
≤160 days	356	[245, 658]	
>160 days	350	[161, 644]	
Number of injections			0.04
2	273	[147, 371]	
3	463	[276, 651]	
4	679	[491, 714]	
5	959	[356, 974]	

Ref, reference value used to calculate P value; N/A, not applicable.

materials available, there is a lack of clear guidelines on their indications and use. Our main objective in this study was to examine the effectiveness of IL in the pediatric population, as well as to compare the different injection materials with regard to post-injection outcomes.

Injection with micronized dermal matrix (Cymetra™, Lifecell Corp, Branchburg, NJ, USA) was performed in 28% of patients receiving a single injection compared to 4% of patients requiring multiple injections (P=0.04). Given that this material has short-term expected duration of benefit (13,14), the surgeon's decision may have been influenced by the clinical severity and expectation of recovery. Notably, the median age for patients receiving an injection containing calcium hydroxyapatite was lower than the median age of patients receiving an injection with micronized dermal matrix (P<0.0001). This suggests that

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there is a preference for using longer lasting injections in younger children. Additionally, the etiology of UVCP did not affect the choice of injection material.

Importantly, differences in post-injection outcomes, including the need for multiple injections, inter-surgical interval, and rates of improvement, were not found to be associated with the type of injection material. Regardless, further study is required to develop standardized protocols for the use of injection laryngoplasty in children. To our knowledge, the ISI between IL procedures has not been studied in children with UVCP. This interval is likely influenced by the expected duration of benefit and the return of pre-injection symptoms in addition to the practice patterns of the treating physician. As there is expected variability in permanence between the different injection materials (8-11), this may suggest that the ISI is more strongly influenced by patient and physician-related factors rather than the duration of benefit of the intervention. Interestingly, the ISI was found to increase as the number of injections increased (P=0.04). Anatomic changes in the vocal fold structure or position following multiple injections resulting in residual medialization may explain the prolonged clinical benefit following repeat injections.

We also examined if earlier intervention could result in improved outcomes or reduce the incidence of subsequent injections. Prior studies have shown that children who underwent IL within 6 months of the onset of UVCP demonstrate improved swallowing outcomes following surgery (15). In contrast, our results did not show a difference in treatment efficacy or ISI in patients receiving earlier intervention. This may be explained, in part, by demographic differences between our study population and that of the referenced study. The patients in our cohort were older at the time of first intervention, which may indicate that early intervention is more critical in younger children.

Our study is limited by its retrospective nature, and thus is dependent on the quality of data recorded in the medical record. Follow up intervals were also inconsistent, making it difficult to ascertain when the symptoms of UVCP returned. Additionally, this study relies on subjective measures of improvement in dysphagia. While a majority (68%) of patients in the study did have a baseline objective measure of dysphagia with a video swallow study or functional endoscopic evaluation of swallow, an additional 11% were diagnosed clinically. However, in our large, diverse pediatric population, certain patients lacked objective post-injection measures, limiting our ability to objectively determine the benefit of this intervention. Though subjective improvement is considered a practical outcome of interest in the pediatric population, this limitation could be addressed through objective pre- and post-intervention swallow evaluation.

The conclusions of this study are limited by the small sample size given that this study examined a total of 44 patients undergoing 97 injections. We are hopeful that this study prompts further research into this topic to generate enough data to develop more standardized practices for injection laryngoplasty in this population.

Conclusions

In this cohort, the type of material injected and patient demographics were not found to be associated with a difference in post-injection outcomes. Further research may help in development of guidelines to aid surgeons in making decisions regarding their choice of injection material and surgical planning.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-21-361/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-21-361/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-21-361/coif). CE is a consultant for Smith and Nephew and Chief Scientific Officer for Zotarix Inc. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Nationwide Children's

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Hospital (No. 00000568) and individual consent for this retrospective analysis was waived.

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